UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/543,122	04/20/2006	Sudha Shenoy	067437-5020US	2631

67374 7590 04/28/2008

MORGAN, LEWIS & BOCKIUS, LLP
ONE MARKET SPEAR STREET TOWER
SAN FRANCISCO, CA 94105

EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
04/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/543,122	SHENOY ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *8-17 and 23-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 18-22* is/are rejected.

7)☒ Claim(s) *3 and 6* is/are objected to.

8)☒ Claim(s) *1-35* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 2/25/08 has been entered in full. Claims 7, 9 and 22 are amended.

Claims 1-35 are pending in the instant application.

Election/Restrictions

Applicants' election of Group I, claims 1-7 and 18-22, in the reply filed on 2/25/08 is acknowledged. Applicants do not indicate whether the election is with or without traverse, but because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 8-17 and 23-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicants' election of the species of (1) Label – fluorescent group; (2) Arrestin – beta-arrestin-2, subspecies EGFP-Barr2-Ub48, corresponding to SEQ ID NO: 6; and (3) GPCR – Class A GPCR, subspecies β2AR in the reply filed on 2/25/08 is acknowledged.

Applicants state that "claims 6, 7, 20 and 22 are readable on the elected species, and claims 1-5, 18-19, and 21 are generic". The Examiner agrees.

Claims 1-7 and 18-22 are under consideration, in so far as they read upon the elected species.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The executed declaration submitted by Applicants on 4/20/06 is defective because the Applicants (Sudha Shenoy and Robert J. Lefkowitz) have each signed the declaration but have not included a date of execution with the signature.

Specification

The disclosure is objected to because of the following informalities:

(1) The disclosure is objected to because the Brief Description of Figure 11 does not refer to each of Figure 11A and Figure 11B, as present in the Drawings filed 7/21/05. See 37 CFR § 1.74, which states "When there are drawings, there shall be a brief description of the several views of the drawings and the detailed description of the invention shall refer to the different views by specifying the numbers of the figures and to the different parts by use of reference letters or numerals (preferably the latter)" and MPEP 601.01(g) which states "if the drawings show Figures 1A, 1B, and 1C and the brief description of the drawings refers only to Figure 1, this is an error in the specification which must be corrected."

(2) An updated priority statement of the instant application's parent provisional and nonprovisional applications should be included in the first sentence of the specification or application data sheet. Specifically, the domestic priority information should indicate that the instant application is a 371 of PCT/US04/02029, filed 1/26/2004. Currently, neither the specification (4/20/06 copy) nor the ADS (7/21/05) includes this.

(3) Page 7 of the specification is objected to for referring to SEQ ID NO: 1-3 as amino acid sequences (lines 20-21) and SEQ ID NO: 4-6 as DNA sequences. The Sequence Listing indicates that SEQ ID NO: 1, 3 and 5 are nucleic acid sequences and that SEQ ID NO: 2, 4 and 6 are the corresponding encoded amino acid sequences.

Appropriate correction is required.

Claim Objections

Claims 3 and 6 are objected to because of the following informalities:

(1) In claim 3, the word "Lysine" should not be capitalized, as it is not a proper name.

(2) Claim 6 is objected to for reciting, "...wherein the modified arrestin further comprises a label..." The specification provides a limiting definition of the term "modified arrestin" on page 20 of the specification: ""Modified arrestin" means an arrestin that has one or more ubiquitin molecules moieties and a label molecule associated or attached to the arrestin". Therefore, the modified arrestin of claim 1 includes already includes a "label".

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-6 and 18-22 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

These claims, as written, do not sufficiently distinguish over the modified arrestin that is produced naturally in cells expressing the β_2-adrenergic receptor (β_2AR) when said cells are contacted with an agonist of the receptor, as evidenced by Shenoy et al, 2001. Science. 294: 1307-1313 (reference C24 on the 6/19/06 IDS). The claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g. by insertion of “isolated” or “purified” or by the recitation of non-natural modifications required to be part of the sequence.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 recites, "The modified arrestin of claim 1, wherein the modified arrestin comprises the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6". It is unclear whether the modified arrestin comprises each of the three sequences, or whether the modified arrestin comprises SEQ ID NO: 2, 4 or 6 (note that the claim does not include the word "or" between the recited sequences).

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7 and 18-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

a modified arrestin comprising SEQ ID NO: 2, wherein the modified arrestin has an increased affinity for a GPCR, as compared to the affinity of a wild-type arrestin, and wherein increased affinity means that the arrestin remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin does not dissociate at or near the plasma membrane,

does not reasonably provide enablement for

a modified arrestin comprising an arrestin or a biologically active fragment of arrestin and a ubiquitin moiety or a biologically active fragment of ubiquitin, wherein the modified arrestin has an increased affinity for a GPCR, as compared to the affinity of a

wild-type arrestin, and wherein increased affinity means that the arrestin remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin does not dissociate at or near the plasma membrane.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is “undue” include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is a modified arrestin comprising an arrestin and a ubiquitin molecule and with the recited functional characteristics (lines 3-6 of claim 1).

The scope of the claims is as follows. The specification teaches that the term "arrestin" encompasses both "naturally occurring" and "engineered variants" of three different types of arrestin (visual arrestin, β-arrestin1 and β-arrestin2). The specification explicitly states that "[b]oth the arrestin and the ubiquitin may include one or more additions, substitutions, mutations, or deletions of amino acid residues (¶19 of the published application). The term "biologically active" broadly encompasses any activity of a molecule, and therefore claim 1 essentially encompasses any fragment of arrestin and/or a ubiquitin (e.g., essentially any fragment of a protein can be used to raise antibodies and is thus "biologically active). Furthermore, the modified arrestin of claim 1 "comprises" such fragments and thus tolerates one or more amino acid changes (including one or more additions, deletions and/or substitutions) anywhere in the sequence of arrestin or ubiquitin. Thus, the "structural" limitation of claim 1 only requires some small portion (as small as a few amino acids) of arrestin or ubiquitin. Furthermore, while the working examples in the specification are directed to an arrestin-ubiquitin fusion protein (chimeric protein), claim 1 encompasses any configuration of arrestin(s)

or ubiquitin(s), bound directly or indirectly, covalently or non-covalently. Thus, structurally claim 1 encompasses a vast genus of modified arrestin comprising various configurations of variants of arrestin or ubiquitin, each of which must be constructed and tested to see if they meet the recited functional limitations (lines 3-6, starting with "has an increased affinity..."). Claims 2-5 and 18, 19 and 21 limit the modified one to with characteristics of ubiquitinated β-arrestin. Claim 6 limits the modified arrestin to one comprising a label. Claim 20 limits the reference GPCR (of the functional limitation) to a "class A GPCR"). Claim 22 recites that the arrestin can be any natural or modified version of the arrestins described above.

In contrast to the scope of the claims, the specification provides limited working examples of a modified arrestin. On page 54, the specification describes a YFP-β-arrestin2-Ub chimeric protein that has increased affinity for the GPCR β2AR, as compared with non-chimeric β-arrestin2. The sequence of this fusion protein appears to be disclosed as SEQ ID NO: 2 and in Figure 2 (and designated 'EYFP-Barr2-Ub'). The specification further discloses two similar constructs designated EYFP-Barr2-Ub48 (SEQ ID NO:4, Figure 9) and EGFP-Barr2-Ub48 (SEQ ID NO: 6, Figure 10). The specification does not clearly describe the nature of these other constructs; however, they appear to have a mutation at Lysine-48 of the ubiquitin protein, which reduces the formation of multi-ubiquitin chains. However, no teachings are provided regarding the influence of this mutation on the affinity of the modified arrestin as compared with wild-type arrestin, which can form multi-ubiquitin chains. As polyubiquitination is part of the process which targets membrane proteins to the proteasome or vacuole for degradation, the skilled artisan could not predict whether permanently monoubiquitinated arrestin would have less, equal or greater affinity than transiently polyubiquitinated arrestin (as occurs with wild type arrestin), and thus these two species belong to the vast genus of variants that would need to be tested prior to using the full scope of the claims.

Furthermore, Applicants have not given any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property, or defined a difference in structure, or difference in function, between the arrestin and ubiquitin

proteins comprised within SEQ ID NO: 2 and variants of each protein. If a modified arrestin comprising variants of the arrestin and ubiquitin proteins of SEQ ID NO: 2 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 2, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 2. Conversely, if a protein variant of SEQ ID NO: 6 need not have a disclosed property; the specification has failed to teach how to use such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al*. (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a

starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al*. (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 18-22 are rejected under 35 U.S.C. 102(b) as being anticipated by Shenoy et al, 2001. Science. 294: 1307-1313 (reference C24 on the 6/19/06 IDS).

The specification defines the term “modified arrestin” as “an arrestin that has one or more ubiquitin moieties and a label molecule associated or attached to the arrestin” (pg 20). However, the term "label molecule" broadly encompasses a ubiquitin molecule, as ubiquitin renders an attached molecule detectable by anti-ubiquitin antibodies. Thus claim 1 encompasses modified arrestin that encompasses an arrestin and a ubiquitin molecule with the following functional characteristic: “increased affinity for a GPCR, as compared to the affinity of a wild-type increased affinity for a GPCR, and wherein increased affinity means that the arrestin remains associated with the GPCR and traffics with the GPCR into endosomes, and wherein the arrestin does not dissociate at or near the plasma membrane”. However, the specification further indicates that the addition of ubiquitin to an arrestin results in this functional characteristic: “the addition of ubiquitin moieties to arrestin increases the affinity of arrestin to binding to a GPCR” (pg 26). Therefore, claim 1 encompasses any ubiquitinated arrestin that associates with a GPCR. Shenoy et al (2001. Science. 294: 1307-1313; cited as reference C24 on the 6/19/06 IDS) teach a modified arrestin that meets the limitations of claim 1. Shenoy et al teach ubiquitinated β-arrestin that associates with the β_2-adrenergic receptor (which is a GPCR), wherein said ubiquitination is required for receptor internalization. Therefore, Shenoy teach a modified arrestin that anticipates instant claim 1.

Ubiquitin is attached to lysines on targets protein by an isopeptide bond, which is a covalent bond, and is inherently susceptible to deubiquitination by deubiquitinating enzymes. Therefore, the teachings of Shenoy described above also anticipate claims 2-4.

The recitation of "5' or 3' end of arrestin" is not limited to any specific residues within arrestin, and therefore broadly encompass the entire protein (i.e., at the very least the 5' end constitutes the first half of the protein from the N-terminal amino acid to the mid-point, and the 3' end constitutes the second half of the protein from the mid-point to

the C-terminal amino acid). Thus the teachings of Shenoy described above also anticipate instant claim 5.

As noted above, ubiquitin itself is a label, and furthermore is an "epitope label" because it is recognized by anti-ubiquitin antibodies (which are well-known in the relevant art). This meets the limitation of "epitope label" in claim 6. Shenoy also teaches that a β-arrestin with a "COOH-terminal Flag epitope". This also meets the limitation of "epitope label" in claim 6. Furthermore, "comprises a label" encompasses direct (covalent) or indirect attachment via binding of secondary molecules. The modified arrestin of Shenoy was detected by "chemiluminescent detection … with Supersignal West Pico reagent (Pierce)", a technique which inherently uses a bound secondary antibody comprising a horseradish peroxidase enzyme, which meets the limitations of both "enzyme" and "chemiluminescent group" in claim 6. Thus the teachings of Shenoy described above also anticipate instant claim 6.

Claim 18 encompasses a modified arrestin of claim 1 with "one or more ubiquitin molecules". Figure 6B of Shenoy shows the ubiquitination of β-arrestin2, including the characteristic "ladder" indicating polyubiquitination. The instant specification provides evidence that this polyubiquitination is a chain of ubiquitins (pg 52, lines 12-13). This polyubiquitin chain is encompassed by "one or more ubiquitin molecules". Thus the teachings of Shenoy described above also anticipate instant claims 18 and 19).

Figure 11B teaches that the beta-2 adrenergic receptor is a "Class A" GPCR. The teachings of Shenoy described above involved use of this receptor, and therefore also anticipate claim 20.

Shenoy further teaches that ubiquitination of β-arrestin is required for internalization of the β_2-adrenergic receptor (pg 1310). Thus the teachings of Shenoy described above also anticipate claim 21.

The arrestin described by Shenoy is β-arrestin2 (see pg 1307). Thus the teachings of Shenoy described above also anticipate instant claim 22.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Elizabeth C. Kemmerer/
Primary Examiner, Art Unit 1646